

Specific and Nonspecific Serum Treatment of Scarlet Fever*

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THE serum treatment of moderately severe scarlet fever is common practice in communicable disease hospitals, and either convalescent serum or antitoxin is generally given by the intramuscular route. The usual dose for the former is 30 cc., and for the latter, one therapeutic dose (6-10 cc.). In some fever hospitals all patients with scarlet fever are treated with serum, and as a rule this is antitoxin. In others serum is administered intravenously whether it be convalescent serum or antitoxin, and although the therapeutic effect is somewhat better and more dramatic, still there is a hazard in such use. At the Herman Kiefer Hospital both sera are used. Prior to 1930 treatment was largely restricted to use of antitoxin, but since that time convalescent serum when available has largely displaced antitoxin because sensitivity to horse serum is thus avoided. There are proponents of both convalescent serum and antitoxin, but the literature reveals no studies carried out on large numbers of patients where both sera were used

during the same epidemic on alternate patients. Such a study was begun August 1, 1936, and carried on for one year. The fiscal year was divided for study purposes into 2 periods of 6 months each, the reason for which will become apparent later.

During the first 6 months, convalescent serum and antitoxin were given to alternate patients who on admission appeared to have exhibited scarlet fever of a moderately severe grade. The determination of the severity of the case and the necessity for serum was the responsibility of two resident physicians (chief and senior) who have been on the Communicable Disease Service for over 10 years. They had no part in the choice of serum to be used. Whenever the serum sensitivity test was positive when antitoxin was to be administered, convalescent serum was given instead, and the case was excluded from the series. The next patient needing serum was given antitoxin if the sensitivity test was negative. Serum was administered in the admitting room prior to removal of the patient to the scarlet fever pavilion.

The scarlet fever convalescent serum used was obtained from recently recovered donors bled in the Department

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of Health Serum Clinic, and each batch of serum represented the contribution of about 10 donors. Thirty-three samples of serum from as many batches were tested for antitoxin content by the Veldee rabbit ear method, and no batch contained more than 2 units per cc. The dose was 30 cc., and a patient received no more than 60 units of antitoxin when convalescent serum was administered. The scarlet fever antitoxin used was obtained from the Laboratories of the Michigan State Department of Health, and each therapeutic dose (10 cc.) contained a minimum of 6,000 units. The ratio, then, of antitoxin in scarlet fever antitoxin to that in scarlet fever convalescent serum was roughly of the order of 100:1.

The data obtained during the 6 month period were the result of treating alternate cases of moderately severe scarlet fever with convalescent serum and antitoxin. The method of serum assignment was expected to result in comparable groups. To try this assumption, the serum groups were tested with respect to the following important characteristics: distribution of cases by month, by age, by temperature on admission to hospital, by day of disease treatment was begun, and finally by the proportion of cases with significant associated conditions. The two serum groups did not differ with respect to the characteristics considered, and for our purpose may be looked upon as comparable in all respects except kind of serum administered.

RESULTS OF TREATMENT FOR THE
6 MONTH PERIOD, AUGUST 1, 1936,
THROUGH JANUARY 31, 1937

During the first 6 months of the study 346 patients with moderately severe scarlet fever were admitted to the Communicable Disease Service. A few patients who belied their real condition upon admission to hospital were

originally in the series but obviously did not belong there because they were of the toxic or septic type necessitating different treatment. The elimination of such cases accounts for the slight discrepancy in the serum group totals. One dose of convalescent serum was given intramuscularly to 177 patients while 169 received one dose of scarlet fever antitoxin by the same route.

Augmented Treatment—Whenever a patient showed no improvement in clinical condition, or the admission temperature had been maintained or risen during a 24 hour period following serum treatment, an additional dose of serum was administered. When this was found necessary, it was charged as a failure against the serum originally administered. Cases with such augmented treatment were excluded from the study in order that the value of one dose of either serum might be determined. In Table I the number of cases in which augmented treatment was necessary is shown for both convalescent serum and antitoxin. Additional serum was administered in 14 cases in which convalescent serum was initially used, compared to 11 patients among the group given antitoxin. One case subtracted from the convalescent group and added to the antitoxin group would change the proportion but slightly, and when tested statistically no significant difference is demonstrated.

TABLE I
Serum Treatment of Scarlet Fever

*Number and Proportion of Cases with
Augmented Treatment by Type
of Serum Used*

<i>Serum</i>	<i>Total Cases</i>	<i>Augmented Treatment</i>	<i>Per cent Aug. Treatment</i>
Convalescent	177	14	7.9
Antitoxin	169	11	6.5

Temperature Pattern — Cases were classified into 3 groups in relation to the effect of serum on temperature. The first group includes cases in which

the temperature declined to normal or to within 1 degree of normal within 24 hours of serum administration, the temperature remaining normal thereafter for a minimum of 5 days. The second group contains cases in which temperatures declined by lysis within 5 days, a reaction considered average for moderate cases of scarlet fever treated without serum. The third group consisted of patients whose fever continued for a period longer than 5 days. When the two sera are compared on the basis of this classification, no noteworthy difference is demonstrated (Table II).

TABLE II

Serum Treatment of Scarlet Fever
Temperature Pattern of Cases by Type of Serum Used

Temperature Pattern	Number of Cases		Per cent of Total Cases	
	C	A	C	A
Normal	88	88	54.0	55.7
Lysis (5 days)	46.	40	28.2	25.3
Con't fever	29	30	17.8	19.0
Totals	163	158	100.0	100.0

Uncomplicated Cases—Scarlet fever is a disease in which complications are quite prevalent, and in general it may be stated that slightly over one-half of the hospital cases of a moderately severe grade will develop complications

of one sort or another. In Table III, the number and proportion of uncomplicated cases are shown by type of serum used. A comparison of the two sera with respect to this factor shows little difference.

TABLE III

Serum Treatment of Scarlet Fever
Uncomplicated Cases by Type of Serum Used

Serum	Total Cases	Uncomplicated Cases	Per cent Uncomplicated
Convalescent	163	70	43.0
Antitoxin	158	68	43.7

Occurrence of Complications—Certain complications occur with greater frequency in scarlet fever than others. The commonest in hospital practice are rhinitis, cervical adenitis, and suppurative otitis media, in the order named. In Table IV the complications noted during the first 6 month period are listed with respect to frequency, proportion, and the type of serum used. Rhinitis and cervical adenitis occurred with the same frequency. The incidence of suppurative otitis media as well as the remainder of the complications shown in the table occurred too infrequently to warrant analysis.

Proportion of Cases with Multiple Complications—The complication analysis was carried one step further by determining the number of complica-

TABLE IV

Serum Treatment of Scarlet Fever
Occurrence of Complications by Type of Serum Used

Complications	Convalescent		Antitoxin	
	No.	Per cent	No.	Per cent
Otitis media, cat.	5	3.1	9	5.7
Otitis media, supp.	9	5.5	11	7.0
Mastoiditis	2	1.2	3	1.9
Ethmoiditis	2	1.2	2	1.3
Rhinitis	65	39.9	63	39.9
Angina, post-scarlatinal	5	3.1
Cerv. adenitis, non-supp.	38	23.3	37	23.4
Arthritis	5	3.1	4	2.5
Carditis	1	0.6	2	1.3
Abscess, soft parts	4	2.5	4	2.5
Paronychia	5	3.1	5	3.2
Bronchopneumonia	1	0.6
Total cases treated	163		158	

TABLE V
Serum Treatment of Scarlet Fever
Number of Complications per Case by Kind of Serum Used

Kind of Serum		Number of Complications per Case					Complications Group			Entire Group	
		1	2	3	4	5	No. of Cases	No. Compl.	Compl. per Case	No. of Cases	Compl. per Case
C	No.	54	29	10			93	142	1.5	163	0.87
	Per cent	58.1	31.2	10.7							
A	No.	50	33	5	1	1	90	140	1.6	158	0.88
	Per cent	55.5	36.7	5.5	1.1	1.1					

tions an individual contracted with relation to the type of serum used. Here again, the differences are not striking (Table V). The frequency and proportion of cases in which one, two, or three complications occurred are practically the same. When only complicated cases are considered, each case has less than two complications, whereas the inclusion of all cases in each serum group shows less than one complication per case.

late release, if the therapeutic effect of serum lasts for an average period of 2 weeks. In Table VI the dismissal status of cases admitted to hospital during the first 6 months is shown by age, number, and proportion of late dismissals, and by type of serum used. An analysis of the table shows that in the antitoxin group a larger proportion of patients aged 1 to 4 and 5 to 9 were detained than in the convalescent serum group. The two age groups in

TABLE VI
Serum Treatment of Scarlet Fever
Dismissal Status of Cases Admitted to Hospital

Age	Total in Group		Late Dismissals		Proportion of Late Dismissals	
	C	A	C	A	C	A
Under 1 yr.
1-4 "	31	32	14	19	45.2	59.4
5-9 "	87	75	23	27	26.4	36.0
10-14 "	16	23	4	3	25.0	13.0
15-19 "	6	11	..	3	27.3
20+	20	17	2	4	10.0	23.5
Totals	160	158	43	56	26.9	35.4

Dismissal Status—Besides the serious complications which might hinder the dismissal of a patient at the end of 14 or 21 days of isolation, such minor conditions as excoriations about the nose and mouth, paronychia, positive cultures from nose, throat, or ear from pre-admission institutional cases were also included as causes for late dismissal. Both convalescent serum and antitoxin in the dosages given could not reasonably be expected to exert much influence on such causes for

question contain the largest number of cases. In the 10 to 14 age group, which is smaller, the reverse is true. The difference would appear to be considerable, but upon testing the data statistically, no significant difference is noted ($p = .38$).

COMMENT

When the therapeutic results of the first 6 months of the study are compared, there appears to be no significant difference between convalescent

serum and antitoxin in the treatment of moderately severe scarlet fever. This type of scarlet fever is one for which serum therapy has always been used at Herman Kiefer Hospital. A control group not treated with serum was not included in the series for this reason. Therefore, from this study, one cannot determine whether without serum there might have been equally good results. Furthermore, the possibility of a nonspecific serum effect was not ascertained. In order to answer these questions a third serum was introduced, on February 1, 1937, and this was used until the experiment terminated on July 31, 1937. The new serum was nonspecific for scarlet fever and contained 1,000 units of diphtheria antitoxin per therapeutic dose of 10 cc. This was furnished by the Laboratories of the State Department of Health and was from horses which had not been used previously in the production of antistreptococcic sera. The nature of the serum was unknown to the hospital medical personnel until after the termination of the study, so that in so far as is humanly possible, no bias was introduced. The 3 sera were given alternately to moderately severe scarlet fever patients as they were admitted to the Communicable Disease Service. Needless to say, the antitoxin and the convalescent serum used during this period were not measurably different from those used during the first 6 months. In the analysis which follows, "special" serum refers to the newly introduced nonspecific serum. When specific serum is mentioned, convalescent serum, antitoxin, or both, are meant.

The data collected during the second 6 months were put to test with respect to comparability of serum groups in a manner similar to that accorded the data of the first 6 months. The 3 serum groups were found to be comparable with respect to the charac-

teristics tested except kind of serum administered.

RESULTS OF TREATMENT FOR THE 6 MONTHS, FEBRUARY 1, 1937,

TO AUGUST 1, 1937

During the last 6 months of the study, 773 patients with a moderately severe type of scarlet fever were dismissed from the Communicable Disease Service. The number of cases was distributed among the 3 serum groups as follows: special serum, 252; convalescent serum, 261; antitoxin, 260. The slight discrepancy in group totals is due, as before, to elimination from each group of toxic and septic cases inadvertently classified as moderately severe on admission.

Augmented Treatment—The number of cases in each group needing additional serum following administration of the initial dose was determined (Table VII). Only 12 and 13 cases receiving convalescent serum and antitoxin respectively needed additional serum; the proportion of such cases is the same. In contrast, the special serum group shows augmented treatment administered to 74, a proportion of 29.4 per cent. When this proportion is compared with that for both convalescent serum and antitoxin, the ratio is nearly 6 to 1. Thus a marked difference is noted in the number of failures as between nonspecific and specific serum therapy. As for the earlier period, failures were eliminated from each group for the remainder of the analysis.

TABLE VII

Serum Treatment of Scarlet Fever

Number and Proportion of Cases with Augmented Treatment by Type of Serum Used

Serum	Total Cases	Augmented Treatment	Per cent Aug. Treatment
Special	252	74	29.4
Convalescent	261	12	4.6
Antitoxin	260	13	5.0

TABLE VIII

Serum Treatment of Scarlet Fever
Temperature Pattern of Cases by Type of Serum Used

Temperature Pattern	Number of Cases			Per cent of Total Cases		
	S	C	A	S	C	A
Normal	79	171	160	44.4	68.7	64.8
Lysis (5 days)	69	46	52	38.8	18.5	21.1
Continued fever	30	32	35	16.9	12.8	14.2
Totals	178	249	247	100.1	100.0	100.1

Temperature Pattern—This factor shows but little variation when the result of specific treatment is compared (Table VIII). There is, however, a striking decrease in the proportion of cases in which the temperature reached normal within 24 hours in the special serum group. The proportion of cases in which the temperature declined by lysis is higher than noted in the specific groups. The proportion of cases with continued fever was slightly greater in the nonspecific serum group.

Uncomplicated Cases—The number of uncomplicated cases in the group receiving special antitoxin was 66 (Table IX). There were 119 uncomplicated cases in each of the convalescent serum and antitoxin groups. The proportions for the various groups were respectively 37.1, 47.8, and 48.2.

It is readily apparent that no difference appears in the proportion of uncomplicated cases in the convalescent and antitoxin groups. The special group again suffers by comparison, and the difference is almost significant ($p = .03$).

TABLE IX

Serum Treatment of Scarlet Fever
Uncomplicated Cases by Type of Serum Used

Serum	Total Cases	Uncomplicated Cases	Per cent Uncomplicated
Special	178	66	37.1
Convalescent	249	119	47.8
Antitoxin	247	119	48.2

Occurrence of Complications—The complications are listed in Table X. When the incidence of the 3 common complications of scarlet fever is compared with respect to the three sera tested, one notes as striking a similarity

TABLE X

Serum Treatment of Scarlet Fever
Occurrence of Complications by Type of Serum Used

Complications	Special		Convalescent		Antitoxin	
	No.	Per cent	No.	Per cent	No.	Per cent
Otitis media, cat.	6	3.4	10	4.0	11	4.5
Otitis media, supp.	20	11.2	13	5.2	15	6.1
Mastoiditis	4	2.2	3	1.2
Ethmoiditis	1	0.4
Rhinitis	88	49.4	95	38.2	86	34.8
Angina, post-scarlatinal	1	0.6	3	1.2	1	0.4
Cerv. adenitis, non-supp.	50	28.1	53	21.3	42	17.0
Cerv. adenitis, supp.	1	0.4
Abscess, peritons	1	0.4
Nephritis	2	1.1	3	1.2	3	1.2
Bacteremia	1	0.6
Abscess, soft parts	2	1.1	4	1.6	5	2.0
Paronychia	3	1.7	7	2.8	9	3.6
Scarlet fever, recurrent	1	0.4
Total cases treated	178		249		247	

TABLE XI
Serum Treatment of Scarlet Fever
Number of Complications per Case by Kind of Serum Used

Kind of Serum		Number of Complications per Case				Complications Group			Entire Group	
		1	2	3	4	No. of Cases	No. Compl.	Compl. per Case	No. of Cases	Compl. per Case
S	No.	59	42	8	3	112	179	1.6	178	1.0
	Per cent	52.6	37.5	7.2	2.7					
C	No.	85	33	10	2	130	189	1.5	249	0.76
	Per cent	65.4	25.4	7.7	1.5					
A	No.	88	31	6	3	128	180	1.4	247	0.72
	Per cent	68.7	24.2	4.7	2.3					

in the incidence rates of these complications for the convalescent and antitoxin-treated groups as was encountered during the first 6 months. Cases receiving special serum show a moderately higher rate for cervical adenitis and rhinitis, and a proportion twice as high for suppurative otitis media. The incidence of the remaining complications listed in the table is too small to warrant consideration.

Proportion of Cases with Multiple Complications—The number of complications per person in the specific serum groups show little variation (Table XI). A smaller proportion of cases receiving nonspecific serum developed but one complication. However, the proportion of cases having two complications was greater for this group. Taken in the aggregate, there is little difference between the serum groups with respect to the number of complications per complicated case.

When all cases in the respective groups are used as the basis for comparison, then the special group shows an average of one complication per case while the specific serum groups show less than one.

Dismissal Status—The remarks previously made with respect to the questionable value of serum on the dismissal status applies equally well to an analysis of the last 6 months' experience. The results previously noted are borne out in Table XII, for although the proportion of late dismissals is higher in the group which received special serum, yet the difference between this group and those receiving specific serum is of slight consequence. The difference between the convalescent serum group and the antitoxin group is practically nil. It will be recalled that on cursory analysis of the first 6 months' experience there appeared to be a real difference in the

TABLE XII
Serum Treatment of Scarlet Fever
Dismissal Status of Cases Admitted to Hospital

Age	Total in Group			Late Dismissals			Proportion of Late Dismissals		
	S	C	A	S	C	A	S	C	A
Under 1 yr.	..	1	1
1-4 "	39	56	57	20	24	25	51.3	42.9	43.9
5-9 "	82	96	116	17	17	19	20.7	17.7	16.4
10-14 "	36	58	48	5	6	4	13.9	10.3	6.2
15-19 "	8	11	6	..	1	3	50.0
20+	13	27	20	3	3	2	23.1	9.1	10.0
Totals	178	249	247	45	52	53	25.3	20.9	21.5

proportion of late dismissals between the convalescent serum group and the antitoxin group, but this was not borne out by test. Thus, the second 6 months' experience is in keeping with that of the first 6 months.

COMMENT

During the last half of the study, 3 sera were used; 1 was nonspecific, and 2 were specific. For all factors tested, specific sera showed better results than did the nonspecific serum. Furthermore, the results obtained with specific serum bear out the experience noted during the first 6 months, namely, that no real difference was demonstrated with respect to their therapeutic value under the conditions of the study. It would appear then that on the basis of the year's study, convalescent serum and scarlet fever antitoxin proved equally effective in the treatment of moderately severe scarlet fever.

It is interesting to conjecture the reason for the similarity in therapeutic effect exhibited by convalescent serum and antitoxin in the doses administered. Several possibilities come to mind. Because this experience covers a single epidemic cycle, one might object that the test period is too short, and that for this reason no real benefit has been demonstrated. The test period might well be extended, but the objection would appear to be less pertinent when the therapeutic result obtained with nonspecific serum is contrasted with that obtained when specific sera were used. The differences in some instances are striking and all are in the same direction, namely, in favor of specific sera. This reason does not appear to be tenable.

A second possibility is the presence in both sera of an antibody other than an antitoxin or an antibacterial substance to which their similar therapeutic effect might be attributed. This is not likely.

A third possibility is that scarlet fever is at present rather mild in Detroit as it is generally in the United States, and that use of either convalescent serum or antitoxin in the dosage used is sufficient to give satisfactory results. This might be interpreted in one of two ways: First, the antitoxin content of both sera is solely responsible for the therapeutic effect obtained. A few workers, particularly Rhoads and Gasul,¹ have implied, if not definitely stated, that the therapeutic value of any scarlet fever serum was entirely dependent upon its antitoxin content. It does not seem plausible that two sera, the ratio of whose antitoxin content is of the order of 100 to 1, should show the same therapeutic results when tested under control conditions. It must be borne in mind that the cases treated in this study were all of the moderately severe type of scarlet fever; all had temperatures ranging between 102° and 105° upon admission to hospital, and all other factors tested were similar. It seems unlikely that the antitoxin content alone determined for both sera the therapeutic results obtained. If this were the case, it would be equivalent to stating that equally good results would be obtained if a therapeutic dose of antitoxin consisting of not more than 60 units were used instead of one containing 6,000 units, the dosage used in this study. This does not appear to be very likely. Second, the therapeutic result demonstrated by antitoxin is due to its high antitoxin content, and a similar result in the case of convalescent serum is due to the presence of antibacterial substances, augmented slightly perhaps by the small amount of antitoxin to be found in this type of serum. This seems the most likely explanation.

SUMMARY AND CONCLUSIONS

The therapeutic effect of scarlet fever convalescent serum, scarlet fever anti-

toxin, and a nonspecific serum was studied during one year beginning August 1, 1936, and ending July 31, 1937. During this time, 995 moderately severe scarlet fever patients were admitted to hospital, and there received a single dose of one of the sera by the intramuscular route. The study was controlled by alternation in administration of sera. No statistical difference was demonstrated between the serum groups when certain status-on-admission factors were tested. From the therapeutic results obtained in this study, the following conclusions are drawn:

1. Convalescent serum and antitoxin in the dosage given and route utilized appear to

exert a similar therapeutic effect with respect to the factors studied.

2. The value a scarlatinal serum exhibits in the treatment of moderately severe scarlet fever does not appear to be gauged entirely by its antitoxin content.

3. If there is value in using nonspecific serum in the treatment of moderately severe scarlet fever, then there is greater value in using specific serum, namely, convalescent scarlet fever serum or scarlet fever antitoxin.

NOTE: The authors wish to express their appreciation to Dr. C. C. Young and Dr. W. A. Bunney for their assistance in the preparation of the scarlet fever antitoxin and the diphtheria antitoxin used in this study.

REFERENCE

1. Rhoads, Paul S., and Gasul, Benjamin M. Convalescent Scarlet Fever Serum and Commercial Antitoxin. *J.A.M.A.*, 102:2005 (June 16), 1934.

Forerunners of Modern Preventive Medicine

THE foundations of the administrative practice of modern preventive medicine are to be seen in the work of the practitioners of medicine in the eighteenth century. The work of Mead has been instanced in this connection, and he was the forerunner of others.

Heberden and Huxham studied fevers; Fothergill described malignant sore throat; Smellie and William Hunter practised and advanced the art of obstetrics; and Charles White applied antiseptic principles to it; Haygarth of Chester introduced notification and isolation of infectious disease; Richard Bradley studied plague at Marseilles; Sir John Pringle began hygienic reform in the British Army; Lind laid

down principles for the abolition of scurvy among seamen and the prevention of typhus fever; Sir George Baker wrote on the cause of Devonshire colic and palsy; Sir Gilbert Blane studied the diseases of the Navy; Percival denounced the lack of hygiene in crowded factory towns and initiated "industrial welfare"; and Edward Jenner introduced vaccination for smallpox in place of the inoculation method practised for seventy years before.

Thus, much research work had been and was being done in fields where the safety of the community and the interest of the practitioner coincided. Walter Elliot, Minister of Health, Health and The State, *Brit.M.J.* Feb. 25, 1939.